Gastric emptying changes are neither necessary nor sufficient for CCK-induced satiety Reference #2

KENT L. CONOVER, STEPHEN M. COLLINS, AND HARVEY P. WEINGARTEN
Departments of Psychology and Medicine, McMaster University, Hamilton, Ontario L8S 4K1, Canada

CONOVER, KENT L., STEPHEN M. COLLINS, AND HARVEY P. WEINGARTEN. *Gastric emptying changes are neither necessary nor sufficient for CCK-induced satiety.* Am. J. Physiol. 256 (Regulatory Integrative Comp. Physiol. 25): R56–R62, 1989.—If gastric emptying plays a significant role in the satiety produced by exogenous cholecystokinin octapeptide (CCK-8) then *1*) the effects on emptying and feeding should share similar kinetics and 2) peptides that inhibit emptying should also inhibit feeding. In the first experiment, CCK-8 (5.6 μg/kg) injected immediately before the introduction of an intragastric load (10 ml saline) or presentation of a test meal (15% sucrose) produced a rapid inhibition of both empyting and feeding. In contrast, the same dose administered 15 min before testing caused no inhibition of emptying, even though it retained the ability to reduce meal size. In *experiment 2*, the abilities of the peptides pentagastrin (100 μg/kg), bombesin (8 and 16 μg/kg), and secretin (2.86, 14.3, and 28.6 μg/kg) to reduce food intake and inhibit emptying were tested. Pentagastrin influenced neither food intake nor gastric emptying. Bombesin caused a small transient delay in emptying but a large and sustained eating suppression. However, a high dose of secretin caused no significant reduction of food intake, in spite of the fact that it inhibited emptying to the same degree as 1.4 μg/kg CCK-8, which does reduce intake. These results suggest that the inhibition of emptying by CCK is not sufficient to explain the satiety effect of CCK-8.

feeding; behavior; kinetics; peptides; cholecystokinin; gastrin; bombesin; secretin

ALTHOUGH THE COOH-TERMINAL octapeptide of cholecystokinin (CCK-8) suppresses meal size (15, 16, 33, 34), the mechanism mediating CCK-induced satiety is not understood. Moran and McHugh (21, 23, 28) have proposed that the satiety produced by CCK-8 depends on the peptide's ability to inhibit gastric emptying. This hypothesis is supported by demonstrations that doses of CCK-8 that suppress meal size also slow gastric empyting in monkeys (23) and rats (1, 2, 7, 11). Although the gastric emptying hypothesis requires these correlational data, findings of this nature do not demonstrate conclusively that the satiety effect of the peptide is mediated exclusively by the inhibition of gastric emptying.

This study uses two approaches to determine the degree to which CCK-induced changes in gastric emptying mediate its satiety action. In *experiment 1*, the kinetics of CCK-8's suppression of emptying and feeding are compared. In spite of the short half-life CCK in plasma [17 min in rats (18)] and in vivo [2–3 min in humans and dogs (38)], exogenous CCK-8 reduces feeding even when administered 15 min before initiation of a test meal (6, 13). If suppression of emptying is critical to the satiety effect of CCK, then inhibition of emptying must also occur 15 min after the administration of CCK.

In *experiment 2* we examine the ability of other gut peptides to affect emptying and satiety. If CCK produces satiety because it slows emptying, then any peptide that inhibits emptying to a degree similar to CCK should produce reduction of food intake of similar magnitude.

METHODS

Subjects

Male Long-Evans hooded rats were bred in the McMaster Psychology Department colony from stock originating from Blue Spruce Farms (Altmont, NY). They weighed 375–500 g at the time of testing. They were housed in individual hanging cages in a colony room maintained at 26°C with a 14:10 h light-dark cycle. Water was available ad libitum and food was provided according to the experimental protocol.

Gastric Cannula Surgery

For both emptying and feeding studies, access to the stomach was provided by a stainless steel gastric cannula implanted surgically (42), under pentobarbital sodium (45 mg/kg) anesthesia. Rats recovered from surgery for a minimum of 14 days.

Injections

Cholecystokinin octapeptide was a kind gift of S. J. Luciana, Squibb Institute for Medical Research, Princeton, NJ (SQ 19 844, no. NN025NC). Pentagastrin (Peptavlon) was purchased from Ayerst Laboratories, Montreal, Canada. Cimetidine (Tagamet) was purchased from Smith Kline & French Laboratories, Canada. Bombesin (B 5508) and secretin (S 5014) were purchased from Sigma (St. Louis, MO). All injections were made up to a volume of 1 ml with 0.15 M saline and were injected intraperitoneally. Control injections consisted of 1 ml 0.15 M saline.

Gastric-Emptying Procedure

Subjects were placed in individual cages (10 × 15 × 25 mm), with a slot in the floor through which the gastric catheter could hang. Rats were 6-h food deprived before

each session, and all tests took place between 1500 and 1700 h.

Before testing, the stomach was cleaned by saline lavage, the gastric catheter was installed, and fluid remaining in the stomach was aspirated. The test load of 10 ml 0.15 M saline was infused directly intragastrically through the gastric cannula at the rate of 10 ml/min. The introduction of the test load into the stomach was designated as *time 0*; the volume of test load remaining in the stomach was measured at 2, 5, 10, 15, 20, 25, 30, 35, and 40 min.

Gastric emptying was monitored using a double sampling method (8). With this procedure each emptying test yielded a complete descripton of the time course of emptying from which half-emptying times could be derived. There were six subjects in each experiment with each subject serving as its own control. Treatment conditions were administered in a random order.

Satiety Procedure

Experimental conditions for satiety tests paralleled those used for emptying tests. Thus animals were 6-h food deprived before each trial with tests performed between 1500 and 1700 h. The gastric cannula was opened and the stomach was flushed with saline lavage. The cannula was reclosed and the animals were returned to their home cages for feeding tests. Animals were fed 15% (wt/vol) sucrose solutions. Experiments were not initiated until the subjects' intakes following control intraperitoneal administration of 1 ml of 0.15 M saline were stable. Sucrose consumption was measured at 5, 10, 15, 20, 25, and 30 min.

Data Analysis

Half-emptying times ($t_{1/2}$) were defined as the time needed for half of the test load to leave the stomach and were derived by fitting the power exponential function to the individual test load time-course data (10). In addition to $t_{1/2}$, the power exponential has the parameter, β, which describes the shape of the emptying curve relative to a simple exponential with the same $t_{1/2}$. When $\beta = 1$, the emptying curve is perfectly exponential. A $\beta < 1$ indicates a faster than exponential initial phase of emptying (i.e., approximately the first 10 min) followed by a slower than exponential phase of late emptying. This type of emptying is characteristic of subjects with impaired pyloric function, as in the case of vagotomy and pyloroplasty (10). A $\beta > 1$ indicates initial emptying slower than exponential followed by a later phase of emptying more rapid than exponential. In this study a $\beta > 1$ is best interpreted as a lag or suppression of emptying in the early phase of gastric emptying. The goodness of fit of the power exponential function to the time courses was measured by the coefficient of determination (R^2); the median R^2 is reported for each treatment. As R^2 approaches 1, the fit of the curve to the data becomes perfect.

To test the effects of dose CCK-8 and injection time on emptying inhibition (*experiment 1*), two-way repeated measures analysis of variance (ANOVAs) (dose CCK-8 by injection time) were performed on the $t_{1/2}$ and β estimates and upon the test load remaining values for 2, 5, and 10 min. Multiple comparisons of the $t_{1/2}$ and β estimates were performed using the Newman-Keuls procedure. To maximize statistical sensitivity to emptying inhibition, the mean remaining test volumes were compared using Dunnett's test (one-tailed) for experimental treatment vs. the control of intraperitoneal saline.

The effects of pentagastrin and cimetidine on $t_{1/2}$, β, and gastric secretion (*experiment 2*) were assessed using two-way repeated measure analysis of variances (ANOVAs). Dunnett's two-tailed test was used for post hoc comparisons of the treatment means. One-way repeated measures ANOVAs were used to analyze the effect of bombesin and secretin on $t_{1/2}$ and β, and multiple comparisons were performed by the Newman-Keuls test.

Feeding data were analyzed with one-way repeated measure ANOVAs on the cumulative sucrose consumptions at 5, 15, and 30 min. Multiple comparisons were analyzed by the Newman-Keuls method.

Peptide Administration Protocols

Experiment 1: kinetics of emptying and feeding inhibition. Cholecystokinin inhibits feeding even when injected 15 min before the initiation of eating (6, 13). We tested whether the effects of CCK-8 on emptying possessed similar kinetics by injecting rats with CCK-8 (5.6 or 11.2 μg/kg) either immediately or 15 min before an intragastric test load of 0.15 M saline.

The satiety effect of CCK-8 under these experimental conditions was assessed by comparing the intakes of 15% sucrose under saline control trials with intakes after injections of 5.6 μg/kg CCK-8 either immediately or 15 min before meal presentation.

Experiment 2: effect of other gut peptides on emptying and feeding. For emptying and feeding studies, all injections were administered immediately before the intragastric load or meal, respectively. To examine the effect of pentagastrin on emptying, subjects received two injections at *time 0* consisting of *1*) saline and saline; *2*) saline and pentagastrin; *3*) cimetidine and saline; or *4*) cimetidine and pentagastrin. Doses used were 100 μg/kg pentagastrin and 5 mg/kg cimetidine. Feeding studies used the identical dose of pentagastrin. To examine the ability of bombesin to inhibit gastric emptying, rats were injected with either saline or that peptide at doses of 8 and 16 μg/kg. Feeding studies with bombesin used the dose of 8 μg/kg only. Studies on the effect of secretin on emptying used 2.86, 14.3, and 28.6 μg/kg, corresponding to doses of 10, 50, and 100 clinical units/kg. Feeding studies only used secretin doses of 14.3 and 28.6 μg/kg.

As indicated, the satiety effect of these peptides was studied under conditions similar to those of the gastric emptying procedure. Each day of peptide administration was preceded and followed by a control saline trial. The satiety effect of the peptides was measured by comparing sucrose consumption on peptide days with the average on saline days.

RESULTS

Experiment 1: Kinetics of Emptying and Feeding Inhibition

Examination of Fig. 1 and statistical analysis of corresponding $t_{1/2}$s (Table 1) revealed that CCK-8 significantly inhibited emptying [$F(2,10) = 42.66$, $P < 0.001$] when injected at *time 0*. Multiple comparisons determined that when injected at *time 0*, both 5.6 μg/kg ($q_3 = 5.81$, $P < 0.01$) and 11.2 μg/kg ($q_6 = 6.18$, $P < 0.01$) CCK-8 significantly raised mean $t_{1/2}$ over that for saline. Emptying inhibition in the early phases of emptying was also indicated by significantly increasing b values with dose [$F(2,10) = 14.55$, $P < 0.001$; see Table 1]. Post hoc comparisons revealed that βs following both 5.6 ($q_4 = 5.81$, $P < 0.01$) and 11.2 μg/kg were significantly higher than control values (respectively: $q_4 = 5.81$, $q_5 = 6.81$, Ps < 0.01).

Injecting the peptide 15 min before the test load significantly reduced the ability of the peptide to inhibit gastric emptying. The mean $t_{1/2}$ after 5.6 μg/kg CCK-8 administered at −15 min was not different from the saline mean at −15 min ($q_3 = 3.90$, NS). Although 11.2 μg/kg CCK-8 injected at −15 min significantly increased half-emptying time compared with saline ($q_3 = 5.30$, $P < 0.01$), the degree of inhibition was significantly less than when the identical dose was injected at 0 min ($q_3 = 5.30$, $P < 0.01$). The reduced ability of CCK-8 to retard emptying when injected 15 min before the intragastric load was also evident in the analysis of β, which revealed that the βs for CCK-8 at both 5.6 and 11.2 μg/kg were not significantly greater than that for saline.

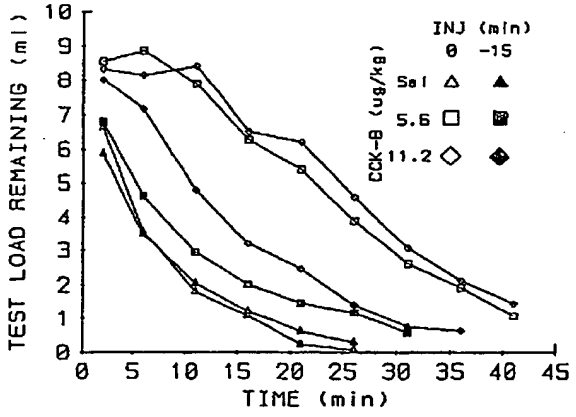

FIG. 1. Time courses for emptying of 10-ml saline (sal) test loads after cholecystokinin octapeptide (CCK-8, 5.6 or 11.2 μg/kg) administered coincident with (0 min) or 15 min before (−15 min) infusion of the test load. Test load remaining is volume remaining in stomach corrected for gastric secretion.

TABLE 1. *Effect of injection time on inhibition of gastric emptying by CCK-8*

	Saline	CCK-8, μg/kg	
		5.6	11.2
	Injection time, 0 min		
$t_{1/2}$	3.9±0.4	20.8±2.3*†	23.5±2.4*†
β^3	0.9±0.06	1.7±0.22*†	1.8±0.22*†
Median R^2	0.99	0.92	0.88
	Injection time, −15 min		
$t_{1/2}$	3.1±0.4	6.3±1.2	10.4±1.4*
β	0.7±0.06	0.7±0.08	1.1±0.06
Median R^2	0.98	0.99	0.98

Values are means ± SE. Mean $t_{1/2}$ is the time at which half the test load had emptied. Injection time represents time at which cholecystokinin octapeptide (CCK-8) was injected relative to infusion of gastric test load. See text for interpretation of β values. * $P < 0.01$ when compared with saline; † $P < 0.01$ when compared with corresponding dose of CCK-8 administered at −15 min.

To be confident that 5.6 μg/kg CCK-8 injected at −15 min did not inhibit emptying, the volumes of test load remaining at times 2, 5, and 10 min after peptide administration were compared with those following saline, using Dunnett's one-tailed test (see Table 2). Stomach values after CCK-8 5.6 μg/kg at −15 min were similar to control values at 2, 5, and 10 min, reinforcing the conclusion that 5.6 μg/kg CCK-8 does not inhibit emptying when administered 15 min before the IG load.

Analysis of sucrose consumption at 5 min (see Fig. 2 and Table 3) revealed that CCK-8 significantly reduced meal size when injected at 0 min ($q_4 = 1.20$, $P < 0.01$), indicating that the peptide acts rapidly. CCK-8 injected coincident with meal initiation also reduced intake at 15 ($q_4 = 2.64$, $P < 0.01$) and 30 ($q_4 = 2.11$, $P < 0.01$) min.

Although the suppression of feeding was significantly reduced following CCK-8 at −15 min compared with 0 min (q_2s = 0.95 and 2.01 at 5 and 15 min, respectively, Ps < 0.01), CCK-8 administered at −15 min (Table 3) did result in significant reductions of intake at 5, 15, and 30 min (q_3s = 1.10, 2.34, and 1.84, respectively, Ps < 0.01), indicating that the satiety effect can persist over a 15-min interval.

The results of *experiment 1* indicate different kinetics of the CCK-induced emptying and feeding effects. The time frame over which CCK influences emptying is brief and consistent with the demonstrated short half-life of the peptide (18, 38). In comparison, the ability of CCK-8 to suppress feeding survives longer intervals.

Experiment 2: Effect of Other Gut Peptides on Emptying and Feeding

Figure 3 and statistical analysis indicated that 100 μg/kg pentagastrin significantly increased gastric secretion during the first 20 min [$F(1,5) = 9.67$, $P < 0.03$], an effect that was blocked by cimetidine [$F(1,5) = 27.98$, $P < 0.005$]. Nevertheless, 100 μg/kg pentagastrin had no effect on the time course of gastric emptying, verified by the absence of significant changes in $t_{1/2}$ [$F(1,5) = 0.02$, NS, or β, $F(1,5) = 0.27$, NS compared with saline trials]. The amount eaten after 100 μg/kg pentagastrin was also not significantly different from control (Table 4). Bombesin (8 and 16 μg/kg) had only a minor impact on the time course of gastric emptying (Fig. 4). Although $t_{1/2}$ values after administration of bombesin were not significantly different from those after saline [$F(2,10) = 1.19$, $P > 0.05$], there was a small, but significant, increase in β at both the 8 μg/kg ($q_2 = 0.17$, $P < 0.05$) and 16 μg/kg ($q_3 = 0.21$, $P < 0.05$), doses. This increase in β, ~20%, is

TABLE 2. *Effect of CCK-8 on test load remaining in stomach at times indicated after intragastric infusion*

Time, min	Saline	CCK-8, μg/kg		Saline	CCK-8, μg/kg		F(2,10)	P
		5.6	11.2		5.6	11.2		
	Injection time, 0 min			*Injection time, −15 min*				
2	6.7±0.3	8.6±0.3†	8.3±0.2†	5.9±0.5	6.8±0.4	8.0±0.3*	3.22	0.082
5	3.6±0.2	8.9±0.5†	8.2±0.2†	3.5±0.2	4.6±0.7	7.2±0.6†	24.62	0.001
10	1.8±0.3	7.9±0.8†	8.4±0.5†	2.0±0.2	2.9±0.5	4.8±0.5†	25.80	0.001

Values are means ± SE of test loads remaining. The time at which the test volumes remaining were measured relative to the onset of infusion. *F* ratios are for injection by time of dose interaction for mean test volumes remaining at 2, 5, and 10 min. Time represents the time at which cholecystokinin (CCK-8) was injected relative to infusion of the test load. Significantly greater than saline at 0 min: * $P < 0.05$; † $P < 0.01$.

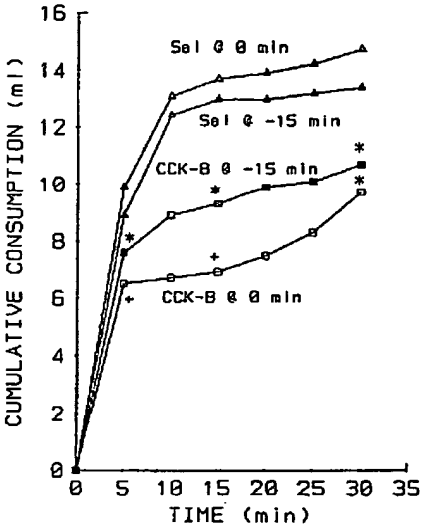

FIG. 2. Cumulative consumption of 15% sucrose after 5.6 μg/kg cholecystokinin octapeptide (CCK-8), administered coincident with (0 min) or 15 min before (−15 min) meal presentation.

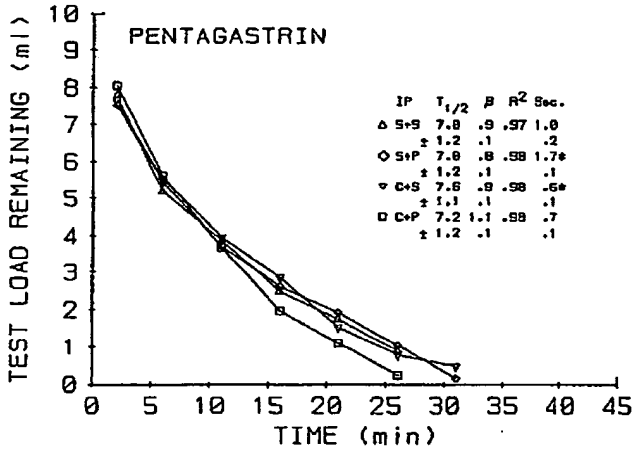

FIG. 3. Time courses for emptying of a 10-ml saline intragastric test load in the following test conditions: S+S, saline + saline; S+P, saline + pentagastrin; C+S, cimetidine + saline; or C+P, cimetidine + pentagastrin. See text for doses and explanation of $t_{1/2}$, β, and R^2 measures. Gastric secretion was measured in milliliters over the 1st 20 min. * $P < 0.05$ Dunnett's two-tailed test.

TABLE 3. *Effect of injection time on CCK-8-induced satiety*

	Consumption, ml		
	5 min	15 min	30 min
	Injection time, 0 min		
Saline	10.1±0.5	13.7±1.0	14.7±0.8
CCK (5.6 μg/kg)	6.5±0.5*†	6.9±0.6*†	9.7±0.8*
	Injection time, −15 min		
Saline	9.2±0.5	13.2±0.8	13.6±0.9
CCK (5.6 μg/kg)	7.6±0.4*	9.3±0.7*	10.6±0.8*

Values for consumption of 15% sucrose are means ± SE. Injection is time at which cholecystokinin (CCK-8) was injected relative to presentation of the test meal. * $P < 0.01$ when compared with corresponding saline condition; † $P < 0.01$ when compared with corresponding dose of CCK-8 when administered at −15 min.

TABLE 4. *Effect of pentagastrin, bombesin, and secretin on consumption of 15% sucrose*

	Consumption, ml		
	5 min	15 min	30 min
Saline	8.0±0.7	10.3±0.7	10.6±0.7
Pentagastrin (100 μg/kg)	7.3±0.7	10.1±0.7	10.7±0.7
Saline	7.7±0.6	10.6±0.8	10.9±0.8
Bombesin (8 μg/kg)	5.1±0.6*	5.4±0.7*	5.7±0.7*
Saline	8.1±0.6	11.0±0.7	11.4±0.6
Secretin (14.3 μg/kg)	7.1±0.6	10.5±0.8	11.7±0.5
Secretin (28.6 μg/kg)	5.3±0.7†	8.1±0.6†	9.3±0.6†

Values for consumption of 15% sucrose are means ± SE. Peptides were injected immediately before presentation of the test meal. * $P < 0.01$ compared with corresponding mean for saline. † $P < 0.01$ compared with corresponding means for saline and smaller dose of secretin.

small compared with the 100% increase produced by CCK-8 in *experiment 1*, suggesting that bombesin produces only a small and transient retardation of emptying. In spite of the small emptying effects, even the lower dose of bombesin, 8 μg/kg, profoundly suppressed eating (Table 4) measured at 5, 15, and 30 min after meal initiation [$F(1,14) = 19.10$, 48.58, and 46.79, respectively, all $P < 0.001$]. The percent suppression produced by bombesin, 49% at 15 min, is similar to the level of inhibition produced by CCK-8.

Secretin significantly inhibited gastric emptying in a dose-related manner, indicated by an increase in $t_{1/2}$ with dose, $F(3,15) = 31.94$, $P < 0.001$ (Fig. 5). Secretin, 14.3 and 28.6 μg/kg, produced elevated but equal increases in $t_{1/2}$ over saline ($q_3 = 4.84$ and $q_4 = 5.25$, respectively, $P < 0.01$). β Values were unaffected by secretin [$F(3,15) = 2.88$, $P > 0.05$)]. The lowest dose of secretin used, 2.86 μg/kg, did not alter the time course of emptying.

Multiple comparisons revealed that only secretin at 28.6 μg/kg significantly reduced sucrose consumption

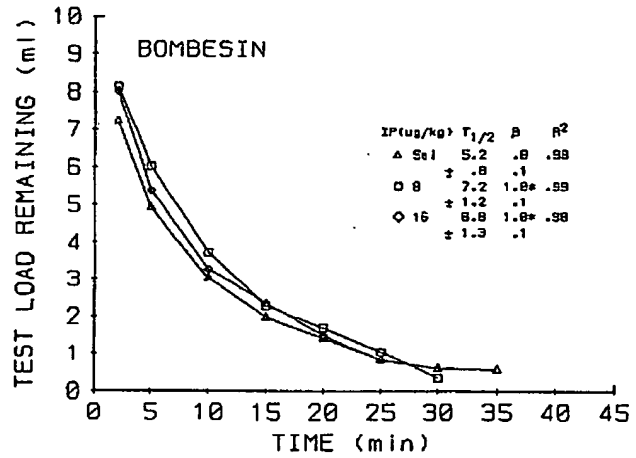

FIG. 4. Time courses for emptying of a 10-ml saline (sal) test load after intraperitoneal (IP) injection of saline or bombesin (8 and 16 μg/kg).

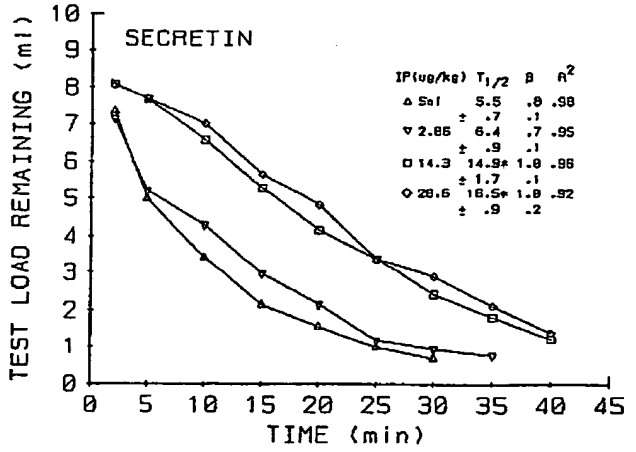

FIG. 5. Time courses for emptying of a 10-ml saline (sal) test load after IP injection of saline or secretin (2.86, 14.3, and 28.6 μg/kg). See text for doses and explanation of $t_{1/2}$, β, and R^2 measures.

(Table 4). Secretin, 14.3 μg/kg, had no significant effect on sucrose intake, even though this dose retards emptying to the same degree as the highest dose of secretin and 1.4 μg/kg CCK-8 (7).

DISCUSSION

The purpose of this study was to examine the importance of gastric emptying in the mediation of peptide-induced satiety. The motivation for these examinations is the necessity of evaluating the most viable hypothesis regarding CCK's mechanism of behavioral action, i.e., that its satiety is mediated by its ability to retard the rate of gastric emptying (21, 23, 28). The results of the current and previous studies (2, 7, 11) demonstrating that CCK-8 suppresses gastric emptying in a dose-dependent manner are consistent with this hypothesis. However, the manipulations employed in this study, which investigate CCKs response kinetics and the ability of other peptides to modulate emptying and eating, demonstrate several important dissociations between the emptying response and satiety. These results are summarized in Table 5 and are discussed in more detail below.

CCK-8 injected coincident with meal initiation produces a dose-dependent inhibition of gastric emptying and meal size. These data are consistent with previous reports of an inhibition of gastric emptying with this peptide (1, 2, 7, 11, 23). This correlation between CCK's effects on emptying and satiety are congenial with the gastric emptying hypothesis. Similarly, the correlation reported in this study between the inability of the structurally related peptide, that pentagastrin to suppress both emptying and eating, is consistent with the predictions of the gastric emptying hypothesis.

The kinetics of the CCK-induced emptying response, however, do not coincide with the kinetics of CCK-induced satiety. Specifically, CCK-8 injected 15 min before the emptying test does not affect the rate of gastric emptying. This observation is consistent with the demonstrated short half-life of the peptide (18, 38). In contrast, administering CCK-8 15 min before a meal preserved a significant and large suppression of food intake. The suppression of feeding behavior when there is no corresponding change in the rate of gastric emptying suggests that changes in gastric emptying are not necessary for CCK-induced satiety. One possible interpretation of these data is that there exists a subpopulation of peripheral CCK receptors responsible for satiety, which are independent of a receptor population mediating CCK-induced emptying changes. Alternatively, the same population of receptors may mediate both responses. However, the time course of the induced emptying changes are comparatively brief, whereas the effect of that peptide on food intake is considerably longer.

The data comparing the effects of bombesin on emptying and satiety further reveal the dissociation between changes in gastric emptying and food intake produced by peptides. Bombesin in a dose of 8 μg/kg produced a profound and reliable suppression of feeding. This finding is consistent with numerous similar demonstrations in the field (6, 19, 37, 41). In contrast, this dose of bombesin produced only a trivial effect on the rate of gastric emptying. The effects of bombesin on gastric emptying reported in the literature have been equivocal. Some (11, 29, 30) have found a decrease in gastric emptying with intraperitoneal bombesin; others (26) have failed to find any effect. It is not clear why different investigators have found different results, although considerations such as dose, species, time of peptide injection

TABLE 5. *Comparison of the effects of gastrointestinal peptides on satiety and gastric emptying*

Treatment	Induces Satiety	Inhibits Emptying
CCK-8 (5.6 μg/kg at 0 min)	Yes	Yes
Pentagastrin (100 μg/kg)	No	No
CCK-8 (5.6 μg/kg at −15 min)	Yes	No
Bombesin (8 μg/kg)	Yes	No
Secretin (14.3 μg/kg)	No	Yes

CCK-8, cholecystokinin octapeptide.

relative to test load, and sensitivity of the preparation used to measure gastric emptying, are all candidates. The current study was designed deliberately so that the protocols used to assess the effects of the peptide on emptying and satiety would be identical. Thus the currently demonstrated dissociation between the effects of bombesin on emptying and satiety demonstrate that changes in stomach emptying are not necessary for peptide-induced satiety. This conclusion with respect to bombesin is not novel, as investigators have already speculated that the mechanism underlying bombesin-induced satiety differs from that of CCK-induced satiety (15).

The secretin data demonstrate that changes in gastric emptying are not sufficient for the induction of satiety. With the use of our preparation, secretin inhibited gastric emptying in a dose-dependent manner, a finding that is consistent with several other reports in the literature relating secretin to gastric emptying (4, 11, 40). In our hands, a dose of 14.3 μg/kg secretin produced an inhibition of gastric empyting identical to that produced by a dose of 1.4 μg/kg CCK-8 (7). However, the critical observation is that the same dose of CCK-8 resulted in a significant inhibition of food intake, whereas 14.3 μg/kg secretin, a dose that retarded gastric emptying to a rate equivalent to that of 1.4 μg/kg CCK-8 (7), produced no satiety whatsoever. These results are consistent with previous reports that secretin does not affect meal size (11, 31).

In summary, these data demonstrate that changes in gastric emptying are neither necessary nor sufficient for peptide-induced satiety. The degree to which changes in gastric emptying contribute to the satiety action of CCK is still somewhat open. The observation that gastric emptying is neigher necessary nor sufficient for peptide-induced satiety does not suggest that in the case of CCK-8 there is no contribution of inhibition of gastric emptying to the satiety effect of the peptide. The current results suggest, however, that the changes in gastric emptying cannot represent the sole mechanism whereby CCK induces satiety in the rat and support other recent reports (7, 22).

In addition to independently verifying previous results, the present study provides new data that address the issue of how CCK-8 induces satiety. The finding that doses of secretin and CCK-8 matched for the inhibition of emptying have differing effects on feeding (*experiment 2*) suggests that comparison of the gastrointestinal responses to these peptides may provide a clue to the basis of CCK's satiety effect. Thus the proposal that contraction of the pyloric sphincter is critical (28) seems unlikely because both peptides induce constriction of the pylorus (12, 25). Moreover, the fact that these hormones produce similar decreases in intragastric pressure (9, 39) indicates that relaxation of the proximal stomach may not account for the behavioral difference. The hormones do vary in their affect on motility of isolated antral muscle, in that CCK-8 causes contraction (3, 14, 24), whereas secretin does not (3, 5, 32). However, antral contractions are not sufficient for the satiety effect of CCK, because gastrin also increases antral motility (3, 14, 32) but has no effect on feeding [*experiment 2*, (20)]. Similarly, the fact that CCK and secretin have opposite effects on intestinal intraluminal pressure (17, 27) cannot account for the CCK-induced satiety, because gastrin produces a pressure increase comparable to CCK (35) without affecting behavior. While tentative, this analysis does not imply that emptying changes are central to feeding control by CCK. Possible mechanisms of CCK-induced satiety may involve a primary effect of the peptide increasing tone in the gastric wall, thereby stimulating vagal afferent fibers or, alternatively, a direct interaction between CCK and its receptors on afferent vagal nerve fibers (43).

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Address for reprint requests: H. P. Weingarten, Dept. of Psychology, McMaster University, Hamilton, Ontario L8S 4K1, Canada.

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